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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/247,874	02/10/1999	GORDON W. DUFF	MSA-004.01	8151

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EXAMINER	
SCHNIZER, RICHARD A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/247,874	DUFF ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34,46-64,70 and 71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34,46-64,70 and 71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 2/9/2005. Claim 71 was added.

Claims 34, 46-64, 70 and 71 are pending and under consideration in this Office Action.

The declaration of Dr. diGiovine was received and entered on 2/9/05.

Rejections Withdrawn

The rejection of claim 53 35 U.S.C. 102(b) as being anticipated by Brennan (US Patent 5,474,796, issued 12/12/95) is withdrawn in view of Applicant's amendment.

Specification

The amendment filed 7/3/2000 stands objected to under 35 U.S.C. 132 because it introduced new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The following text is reproduced from the Office Action of 9/9/04.

The added material which is not supported by the original disclosure is as follows:

The amendment to page 4, line 27 changing guanine to cytosine is new matter.

The amendments to page 6 lines 32 and 33, page 10, line 11, page 37, line 8, and page 38, line 8, requiring substitution of cytosine (c) for guanine (G) and vice versa, are new matter.

The amendment at page 38, line 11 replacing "2" with --1-- is new matter.

Figure 2D filed 2/8/2002 comprises new matter in that it comprises a C residue at position 6912.

The Sequence Listing submitted 1/26/04 comprises new matter in that it comprises as C residue at position 8845 of SEQ ID NO:2.

In support of the preceding amendments, Applicant previously argued that the indication in the specification as filed that alleles 1 and 2 comprised C and G residues, respectively, at position 6912 was an inadvertent error, and that alleles 1 and 2 actually comprised a G and C residues, respectively at position 6912. This argument was subsequently supported by the declaration of Dr. di Giovine on 3/2/2001. The declaration indicated that the prior art taught a G at position 6912, that a C had been discovered by Applicant, and that Applicant had named the prior art allele comprising G at 6912 as "allele 1" and the allele comprising C at 6912 as "allele 2". The declaration was supported by output from an automated nucleic acid sequencer showing approximately 340 bases of sequence, including a C at position 199, which appeared to correspond to position 6912 of the IL-1 beta sequence. Declarant also indicated that the specification taught that allele 1 was the more frequently occurring allele in nature, and so it could be considered the wild type allele.

In response the PTO noted the following. There is no doubt that Applicant has discovered that there is a polymorphism at position +6912 of the IL-1B gene. There is no doubt that the previously published sequence had a guanine at +6912 and that Applicant amplified a portion of an IL-1B gene and discovered a cytosine at +6912. However, Applicant's arguments and the declaration do not provide sufficient evidence

to show that Applicant was in possession of amended SEQ ID NO:2, and the sequence set forth in amended Fig. 2, at the time of filing. These sequences are 9721 bases in length, and differ from the prior art IL-1B sequence (GEN XO4500) only at position +6912, which has been converted to C from G. However, neither the specification nor declaration as filed supports a 9721 nucleotide sequence of IL-1B with a C at the +6912 polymorphic site. The originally filed SEQ ID NOS: 1 and 2 and Figures 1 and 2 all disclosed a G at +6912. The specification at page 36 shows that the polymorphism was detected on a 403 base PCR fragment of the IL-1B gene, and the declaration of 3/2/01, shows about 340 bases of sequence comprising the polymorphism. This does not provide support for the 9721 bases of sequence in amended SEQ ID NO:2 and Fig. 2 that have a C residue at the polymorphic position. Since polymorphisms can occur throughout a molecule, one cannot assume that there are no other polymorphisms linked to position +6912 within the 9721 bases of the IL-1B gene, and that the sequence of the rest of the 9721 nucleotides is identical to that reported in the prior art. As such, absent supporting evidence, one cannot simply assume that the Applicant was in possession of amended SEQ ID NO:2, or Fig. 2, at the time of filing. The declaration fails to provide such evidence.

In addition, the changes to the specification which reverse the designations of "allele 1" and "allele 2" appear to represent new matter. Applicants state in the arguments "the sequencing revealed a novel G to C mutation that is referred to herein as the IL-1B(+6912) allele 2." There is no disclosure in the specification to indicate that this is the case. The specification as filed does not refer to the "C" allele of this

polymorphism as allele 2, instead it very clearly defines the "C" allele of this polymorphism as allele 1 (See specification page 6, line 31 and specification page 38 line 11 which exemplifies a probe to allele 2). It is established that "An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction (MPEP 2167.03(II))." Thus, one must determine whether or not the correction of the specification herein is an obvious error.

Applicants assert in the di Giovine declaration that the "cytosine" allele of the disclosed polymorphism was referred to in the laboratory as "allele 2" of the two possible polymorphic alleles (declaration ¶ 6). However, this is not supported by the specification. The specification very clearly identifies allele 1 as being the cytosine allele and allele 2 as being the guanine allele on page 6, line 31, and is consistent with this definition throughout. The examples teach the amplification of a 403 bp fragment of the 3'UTR of the IL-1B gene and sequencing of the gene and discovery of a novel C to G polymorphism (Example 1, beginning on p. 37).

Applicants teach in example 2 that the IL-1B allele 2 was found in a population of 820 individuals at a frequency of 0.266. In the declaration, applicants state that "allele 1 is the more frequent allele and may therefore be considered the wild-type allele." In this example applicants teach a probe for allele 1 (SEQ ID NO: 8) which has a "C" at the polymorphic position, and a probe for allele 2 (SEQ ID NO: 9) which has a "G" at the polymorphic position. The remainder of the examples refer only to the alleles by their numerical identifiers.

A possible explanation for the disclosure in the specification which is consistent with the data and examples presented in the specification is as follows:

(a) There is a known version of the IL-1B gene which has a G at position +6912.

(b) Applicants sequenced a PCR fragment of the 3' UTR containing this position.

(c) Applicants discovered a C at this position in the PCR fragment.

(d) Applicants screened a population of 820 people and discovered that the "C" allele is more frequent. Applicants assigned the arbitrary designator "allele 1" to the "C" allele. Applicants assigned the arbitrary designator "allele 2" to the "G" allele.

Applicants have provided another possible explanation of the specification which is contingent upon a recognition that there was an error to begin with. It is not clear from the specification as filed that applicant even erred in their reference to the particular alleles. In fact, the specification as filed appears to be totally consistent with itself in reference to allele 1 and allele 2 as being a "C" for allele 1 and a "G" for allele 2. Thus, it does not seem that the error would have been recognized on its face by a reading of the specification by one skilled in the art, and more to the point, even if the error were clear, the solution to the problem is not readily apparent from a reading of the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Response to Arguments

Applicant's arguments filed 2/9/05 have been fully considered but they are not persuasive.

Applicant addresses the objection at pages 5-7 of the response, and through the declaration of Dr. diGiovine submitted 2/9/05, including pages from a laboratory notebook. Applicant's arguments, and the declaration, are not persuasive because no evidence is presented that supports the idea that Applicant actually intended to name the G-containing allele "allele 1" and the C-containing allele "allele 2." In fact, the available evidence supports the opposite conclusion.

The Examiner concurs with items 1-5 of the Declaration of Dr. diGiovine. Items 6, 9, and 10 of the declaration, discussed at pages 5-7 of the response, bear directly on the issue of whether or not amendments to the specification that switch the identities of IL-1B +6912 alleles 1 and 2 introduce new matter.

In item 6, it is indicated that a G to C change at the +6912 location was determined by sequencing, and the reader is referred to page 116 of the Notebook. Page 116 shows output from a sequence analyzer that contains a G residue at the position corresponding to +6912. This does not support identification of the 'G' allele as allele 1, because the notebook does not indicate that the sequenced allele was allele 1. Furthermore, the Notebook at page 116 discusses assay for determining the genotype at +6912 by restriction digest in which G,G genotypes give bands of 89, 76, and 61 bases, C,C genotypes give bands of 76, 61, 54, and 35 bases, and G,C heterozygotes give bands of 89, 76, 61, 54, and 35 bases. This corresponds precisely with the specification at page 37, lines 31-35 which states that a band pattern of 89, 76, and 61 bases identifies IL-1B allele 2, a pattern of 76, 61, 54, and 35 base bands identifies IL-1B allele 1, and heterozygotes show all five fragments. Thus page 116 of the Notebook

provides support for the position that Applicant correctly identified the +6912 G allele as "allele 2", and the +6912 C allele as "allele 1", in the originally filed specification. Similarly, page 122 of the Notebook correlates with the specification at page 45 in Table 3. Specification Table 3 shows that IL-1 B +6912 allele 2 is tightly linked with IL-1B(TaqI) allele 2 (position +3954). This is consistent with page 122 of the laboratory notebook which, according to declaration item 9, is also a linkage analysis of the IL-1B +6912 and IL-1B taq loci. Page 122 of the notebook shows that Taq genotype "1/1" correlates with +8845 genotype "CC", and Taq genotype "2,2" correlates with +8845 genotype "GG". As noted by Applicant, position 8845 of SEQ ID NO:1 corresponds to position +6912 of the IL-1B gene. The analysis on Notebook page 122 concludes: "Thus it appears that Allele (G) of my polymorphism is 100% associated with allele 2 of allisons Taq – and C is 100% linked to allele 1." Thus, both page 122 of the Notebook and original Table 3 from the specification indicate that the +6912 C and G alleles were associated with IL-1B Taq alleles 1 and 2, respectively. The amendments to the specification, would reverse these associations such that +6912 C and G alleles were associated with IL-1B Taq alleles 2 and 1, respectively. There is no evidence in the response, the declaration, or the Notebook that supports this reversal of identities. The statement of Dr. diGiovine in item 10 of the declaration that he believes that one of skill in the art would recognize the existence of a typographical error based on the teachings of the specification and contents of the Notebook is unpersuasive for the reasons discussed above, i.e. the evidence in the Notebook supports the opposite conclusion. The statement of Dr. diGiovine that measurements of allele frequency

demonstrating that allele 1 occurs more frequently than allele 2 do not provide evidence that allele 1 is the G allele, because as stated in the objection, it is possible that the C allele is more prevalent in the population that was assayed. Declarant's assertion that the sequence of Clark (containing the G residue) is the wild type is supported by reference US Patents 5686246, 6720141, 6730476, and 6746839 and GenBank Accession No. P01584. US Patent 5686246 does not contain the phrase "wild type". US Patents 6720141, 6730476, and 6746839 do not appear to contain a reference to the sequence of Clark, and do not appear to contain any assertion that such a sequence is wild type. The Examiner was unable to find any evidence that GenBank Accession No. P01584 identifies the sequence of Clark as wild type. Applicant has failed to point to any specific passage in any of these documents for support.

Items 6-10 of the declaration, and pages 5-7 of the response are unpersuasive as they relate to the issue of whether or not Applicant had possession of a 9721 base nucleic acid containing a C residue at position 8845 at the time the invention was filed. Applicant argues in the declaration and the response that identification of a 403 base PCR fragment containing the C residue in the appropriate sequence context is sufficient, and there is no reason to resequence the rest of the gene. This is unpersuasive because it is unsupported by evidence, and because it does not address the issue of what Applicant was in possession of at the time of the invention. The specification as filed did not contain a 9721 base sequence with a C at position 8845, and Applicant has presented no evidence to the contrary. The following hypothetical situation is instructive. Applicant's disclosure shows that the +6912 polymorphism is

associated with the Taq polymorphism at position +3954 in more than 99% of assayed samples. If one identified the non-wild type version of the +3954 polymorphism on a 400 bp PCR fragment when the only other sequence known was the 9721 base sequence of Clark (SEQ ID NO:1), would one have been in possession of a sequence identical to that of Clark except for the difference at position +3594, or would one have been in possession of a sequence identical to that of Clark except for a differences at both +3594 and +6912, even though the +6912 polymorphism was unknown at the time the +3954 polymorphism was discovered? The answer is that one would have been in possession of neither sequence unless it was completely disclosed because one cannot predict the nature of the DNA sequence, it must be determined empirically as evidenced by the existence of the +6912 polymorphism. For these reasons the objection is maintained.

Claim Objections

The objections to claims 56, 57, and 70 are overcome by Applicant's amendments.

Claims 54 and 55 stand objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 54 and 55 are drawn to the isolated nucleic acid of claim 46 further comprising a label, or bound to a solid phase support. However, claim 46 is drawn to an isolated nucleic

acid **consisting of** a nucleic acid sequence. The claim uses closed language to describe the nucleic acid. As a result, claims 54 and 55 do not further limit the isolated nucleic acid set forth in claim 46, instead, they improperly add matter which is not accounted for in claim 46, i.e. a label or a solid support. Because they do not further limit claim 46, but instead broaden it, claims 54 and 55 are improper dependent claims.

Response to Arguments

Applicant's arguments filed 2/9/05 have been fully considered but they are not persuasive.

Applicant asserts that claims 54 has been amended to independent form. This is incorrect. Claim 54 depends from claim 46, while claim 55 depends from claim 54.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 71 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 71 is indefinite because it recites a non-sequitur. Claim 71 requires simultaneously that the claimed nucleic acid must comprise about 100 consecutive nucleotides of SEQ ID NO:1, including position 8845, but also requires that position 8845 must differ from that in SEQ ID NO:1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 34, 46-64, 70, and 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 34, 46-64, and 70 are drawn to SEQ ID NO:2, or to fragments thereof comprising position 8845 (which is the same as IL-1B position +6912 discussed above). As discussed at length above, one of skill in the art could not have come to the conclusion that Applicant was in possession of SEQ ID NO:2 (as amended) at the time the invention was filed. SEQ ID NO:2 as amended is 9721 bases in length and contains a C residue at position 8845 that has been identified as a polymorphic position. However, the specification as filed did not disclose a 9721 nucleotide sequence with a C at position 8845, and the addition of such a sequence to the disclosure represents new matter such that one of skill in the art could not come to the conclusion that Applicant was in possession of SEQ ID NO:2 at the time of the invention.

Claim 71 is drawn to a nucleic acid consisting of about 100 consecutive nucleotides of SEQ ID NO:1 and containing a C at position 8845 when numbered in accordance with SEQ ID NO:1. The specification as filed did not disclose any nucleic

acid consisting of about 100 consecutive nucleotides of SEQ ID NO:1 and containing a C at position 8845, so this claim introduces new matter.

Response to Arguments

Applicant's arguments filed 2/9/05 have been fully considered but they are not persuasive.

Applicant addresses the rejection at page 8 of the response, and through the declaration of Dr. diGiovine submitted 2/9/05, including pages from a laboratory notebook. Applicant's arguments, and the declaration, are not persuasive for the reasons set forth above under Specification.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.

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